Best Practice & Research Clinical Anaesthesiology 33 (2019) 199–209

Contents lists available at ScienceDirect

Best Practice & Research Clinical Anaesthesiology

journal homepage: www.elsevier.com/locate/bean

7

Closed-loop hemodynamic management

Brenton Alexander, Doctor (MD) [a, 1],
Joseph Rinehart, Doctor (MD) [b],
Maxime Cannesson, Professor (MD PhD) [c],
Jacques Duranteau, Professor (MD PhD) [d],
Alexandre Joosten, Professor (MD PhD) [d, *]

[a] *Department of Anesthesiology, University of California, San Diego, CA, USA*
[b] *Department of Anesthesiology & Perioperative Care, University of California Irvine (UCI), 101 the City Drive South, Orange, USA*
[c] *Department of Anesthesiology & Perioperative Medicine, David Geffen School of Medicine, 757 Westwood Plaza, Los Angeles, CA, USA*
[d] *Department of Anesthesiology and Intensive Care, Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, Université Paris-Saclay, Hôpital De Bicêtre, Assistance Publique Hôpitaux de Paris (AP-HP), Le Kremlin-Bicêtre, France*

Keywords:
automation
vasoconstrictor agents
fluid therapy
intraoperative monitoring

As the operating room and intensive care settings become increasingly complex, the required vigilance practitioners must dedicate to a wide array of clinical systems has increased concordantly. The resulting shortage of available attention to these various clinical tasks creates a vacuum for the introduction of systems that can administer well-established goal-directed therapies without significant provider feedback. Recently, there has been an explosion of academic exploration into creating such automated systems, with a strong specific focus on hemodynamic control. Within this field, the largest focus has been on goal-directed fluid therapy as systems automating vasopressor administration have only recently become viable options. Our goal in this review article is to summarize the validity of the relevant goal-directed hemodynamic systems and explore the expanding role of automation within these systems.

* Corresponding author. Department of Anesthesiology and Intensive Care, Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, Hôpital De Bicêtre, Assistance Publique Hôpitaux de Paris, 94270, Le Kremlin-Bicêtre, France.
E-mail addresses: bsalexander@ucsd.edu (B. Alexander), joosten-alexandre@hotmail.com, alexandre.joosten@aphp.fr (A. Joosten).
[1] Fax: +1619534 5424.

https://doi.org/10.1016/j.bpa.2019.04.003
1521-6896/

Introduction

One of the fastest changing aspects of perioperative medicine is the relationship anesthesia providers have with the increasingly complex devices that surround them in the operating room (OR). Although our field once consisted of a medical practitioner providing ventilation, sedation, and monitoring through a simple facemask artfully dribbled with ether, it has now evolved into an environment where we are surrounded by a wide array of increasingly complex and sophisticated physiological technologies. As a result, many perioperative physicians and practitioners do not *completely* understand the devices they rely so heavily upon [1,2]. The theoretical long-term conclusion of this evolution is perioperative systems that are largely independent of practitioner intervention for frequent, repetitive actions (relying instead on practitioner input for more high-level goal selection and navigation of the anesthetic). In theory, the standardization and vigilance gained from such an arrangement could – just as it has in the airline industry–lead to lower complication rates, reduced patient morbidity and mortality, and lower costs. Although it is an interesting concept to discuss, such elaborate systems will likely not exist for many decades.

That being said, steps toward automating individual aspects of perioperative patient care are underway and one category receiving large amounts of interest is hemodynamic optimization. The reasons for this particular expansion are plentiful but largely consist of advancements in computing, development of a plethora of perioperative monitoring devices, evidence-based data-driven protocols, reduced physician workload, and improved affordability. Automation of hemodynamic control has mainly been focused on two areas: fluid delivery and vasopressor administration. Significantly more literature addressing the automation of fluid therapy has been disseminated, as various goal-directed fluid therapy (GDFT) protocols known to decrease perioperative morbidity have become widely accepted. Additionally, vasopressor automation is also gaining traction and will likely continue to expand in the upcoming years. Our goal here is to provide an overview of the recent evidence addressing various closed-loop systems designed to optimize perioperative hemodynamics.

The rationale for hemodynamic targets and protocols

Before discussing the merits of automation, it is important to first ask if we have something worth automating. Do the protocols at the backbone of closed-loop systems actually improve our patients' outcome? The general theory underlying these protocols is that a large proportion of perioperative complications are related to the imbalance of oxygen supply and demand, which is affected significantly by tissue hypo- and hyperperfusion [3]. To avoid such perfusion abnormalities, which are very difficult to directly quantify, perioperative physicians have subsequently aimed to optimize the best available hemodynamic surrogates. These include arterial pressure, cardiac function, fluid status, end organ function, oxygenation, and many other clinical variables known to affect oxygen delivery. Using these targets, the overarching strategy of goal-directed hemodynamic therapy (GDHT) is to decrease suspected malperfusion through the clinical optimization of fluid status, vasopressors, and inotropes [4]. As stated above, the majority of recent hemodynamic optimization literature has been focused on GDFT and its ability to decrease patient morbidity. Although there has been increased focus on goal-directed vasopressor and inotrope administration, it will likely still require future academic investigations to completely rationalize its widespread implementation.

What do the data show regarding both GDFT and GDHT? Fortunately and unfortunately, the technological and physiological end points used in most studies are updated at an incredible rate. When examined individually, older literature contains protocols, devices, and/or statistical approaches that are significantly outdated or irrelevant to modern hemodynamic therapy. When examining modern data, the overall picture is also slightly blurry. Currently, there is a strong trend toward improved morbidity, although it may be potentially less-so than previously thought. A large, randomized, prospective trial in 2014 ("OPTIMISE") indicated that the clinical benefits of GDHT may have been previously overstated [5]. Interestingly, the same trial, when integrated into a large meta-analysis of 38 previous trials, demonstrated decreased perioperative morbidity, decreased length of stay (LOS), and even a strong trend toward a statistically significant decrease in mortality for patients cared for with GDHT [5]. Two studies published around the same time also concluded that GDHT may be less clinically advantageous than that previously believed [6,7], although advances in control groups' "baseline" fluid therapy may have reduced the impact of protocolization. Additionally, it is worth clarifying that the strongest data supporting the use of GDHT have largely been in high-risk surgical patients [8,9], as low-to moderate-risk surgeries require significantly larger sample sizes to demonstrate meaningful clinical benefit.

Beyond the above-mentioned large meta-analysis in 2014, additional recent evidence has also emerged in support of establishing GDHT protocols. The most significant of these being a randomized, multicenter, prospective trial that found a 50% decrease in moderate to severe complications (acute kidney disease, pulmonary edema, respiratory distress syndrome, wound infections, etc.) and a decreased length of hospital stay in the GDHT group [10]. The reduction in complications was isolated to patients undergoing gastrointestinal procedures, although that was 75% of the patient population included in the study. Other smaller studies have also been recently completed that are worth discussing. One group from the University of California, Irvine, demonstrated decreased LOS and morbidity with GDHT implementation through a historical, prospective, quality improvement (QI) study [11]. In another recent QI study, Jin et al. found decreased morbidity but no decreased 30-day mortality, LOS, or cost associated with the implementation of a GDFT program using a pre- and post-implementation comparison [12]. In another match-controlled study, Russo et al. found decreased fluid administration, increased intraoperative diuresis, lower postoperative lactate levels, shorter times to bowel recovery, and decreased LOS for surgical gynecologic patients maintained with GDHT managements, which included both fluid and vasopressor/inotrope support [13]. Finally, Lima et al. demonstrated that the implementation of a hemodynamic protocol resulted in a significant decrease in postoperative complications compared to standard-of-care therapy [14].

When solely examining vasopressor administration independent of a fluid therapy protocol, the evidence is less robust. Importantly, to justify the potential automation of vasopressor administration systems, it is important to examine the efficacy of manually titrated vasopressor administration. Although there are multiple previous studies indicating that keeping a patient within a target range is difficult, quantifying the actual discrepancies has proven to be quite challenging [15–19]. Fortunately, one group has recently completed such a study at two large international academic centers examining patients in both the intensive care unit (ICU) and the OR under vasopressor therapy. This study demonstrated that patients remained only in the desired blood pressure target range for 48% of their vasopressor administration period, with most patients being kept above the target range (likely allow for a buffer if provider vigilance diminished) [20].

Moving beyond this unacceptable efficacy of manually titrated vasopressor infusions, there have been multiple studies highlighting the importance of perioperative blood pressure control in the OR [18,21–25] and ICU [17,26–29]. The combination of both a demonstrated benefit and a poor provider control is alarming and clearly justifies the need for further research into the development of novel systems that can improve vasopressor administration.

When looking at all of these data cohesively, it appears that GDHT protocols do consistently decrease perioperative morbidity in moderate- and high-risk surgical patients, although conclusive effects on LOS and mortality still require additional clinical research. Furthermore, there is sufficient evidence that automating vasopressor administration in the OR and ICU would provide significant improvements in blood pressure management and potentially patient outcome.

Benefits of automation: increased protocol adherence and decreased variability

Because of the strong evidence of decreased morbidity and moderate evidence for decreased LOS and mortality, implementation of these GDHT protocols should already be widely accepted in the anesthesia community. Unfortunately, the amount of moderate-to high-risk anesthetics administered worldwide that have successfully employed and reported their GDHT results is remarkably limited. This can be due to many issues, including increased initial workload, cost, clinician acceptance, fear of computer-physician replacement, and/or internal results not being reported.

What options do we have for improving adherence to these clinically beneficial GDHT protocols? Additional education is always an option, but this approach is time consuming, and the concepts behind GDHT are relatively straightforward and should already be understood by most practicing clinicians. The necessary technology is already standard in most first-world ORs and ICUs. It is important to also note that many trials have demonstrated extremely large variability in fluid administration in the OR and ICU, with extremes of fluid therapy being associated with increased morbidity [30–32]. This variability is the nemesis of protocolized treatment and has been found to be largely due to provider-specific preferences and is further complicated by a lack of vigilance and evidence-based knowledge [33]. Such variability was at the heart of implementing and maintaining GDHT protocols within various institutions and governments worldwide. Unfortunately, as anyone who works in a large hospital system can undoubtedly understand, the adherence to these protocols themselves has large variability and an overall poor compliance [11,34–36]. This is consistently true even with data-associating improved compliance of enhance recovery after surgery (ERAS) protocols with decreased LOS, 30-day mortality, and readmission rates [37,38]. It now appears apparent that this problem of poor adherence to GDHT protocols must be addressed by a more fundamental change in the perioperative physician's tool belt.

Luckily, as computing has advanced, “automation,” a novel and efficient approach to this problem, has emerged. The definition of automation in this context includes any system that uses real-time information to partially or completely guide therapeutic interventions, which includes both closed- and open-loop technology. Closed-loop systems are completely automated and use input variables (physiological variables in this context) to change output variables (fluid, vasopressors, and inotropes in this context) without the required input of clinicians. Open-loop systems do the same task but require a minimal amount of clinician input before therapies being automatically initiated or adjusted (e.g., final approval before actually administering the fluid bolus or adjusting the vasopressor infusion rate). Removing all or most aspects of repetitive provider workload, combined with the incredible ability for computer systems to never lose vigilance and make thousands of observations and adjustments every second, has allowed for vastly improved compliance and decreased variability and is even starting to independently demonstrate improved outcomes for patients treated with GDHT systems.

Additionally, closed-loop systems have recently been shown to better maintain a hemodynamic target within a desired range, through a decrease in overshooting and undershooting of physiological end points, all while decreasing physician workload and increasing compliance to GDHT protocols [39,40]. Additionally, closed-loop GDFT systems have been shown to increase cardiac output when compared to manually adjusted hemodynamic therapy [41].

What do these GDHT systems look like? Typically, there is a computer with input connections to a patient's hemodynamic data and output connections to one or more protocolized interventions (fluid therapy, vasopressors, and/or inotropes). As the case progresses, the computer has software that is constantly (usually many times per second) analyzing the collected data and using well-established GDHT protocols to adjust the output interventions. In its simplest form, these systems are perfectly positioned to increase adherence to established GDHT protocols, while also decreasing provider workload. Fig. 1 presents an OR in Erasme Hospital, Brussels, Belgium, where the entire anesthetic was managed using several closed-loop systems operating in parallel.

One particularly frequent question perioperative clinicians propose regarding closed-loop technology is: “Will this automation eventually replace me in the operating room?” In other words, because of the recent development of extremely sophisticated 21st-century perioperative monitoring devices, could closed-loop systems expose the specialty of anesthesiology to substitution by robots coupled or not with artificial intelligence? As stated elsewhere, our research group feels that a more appropriate question would be: “What benefit could automation have on my daily clinical practice and how could this system improve patient care while also mastering mundane clinical tasks?” We do not yet have a finalized answer to this question, but research on the subject is being reported at an unprecedented rate. Closed-loop hemodynamic systems that utilize a validated decision support system, implemented alongside the knowledge and expertise of a well-trained perioperative clinician, will help to ensure that the highest quality of care is being employed consistently and effectively for all patients. Finally, it is important to keep in mind that the patient, not the computer, must always come first.

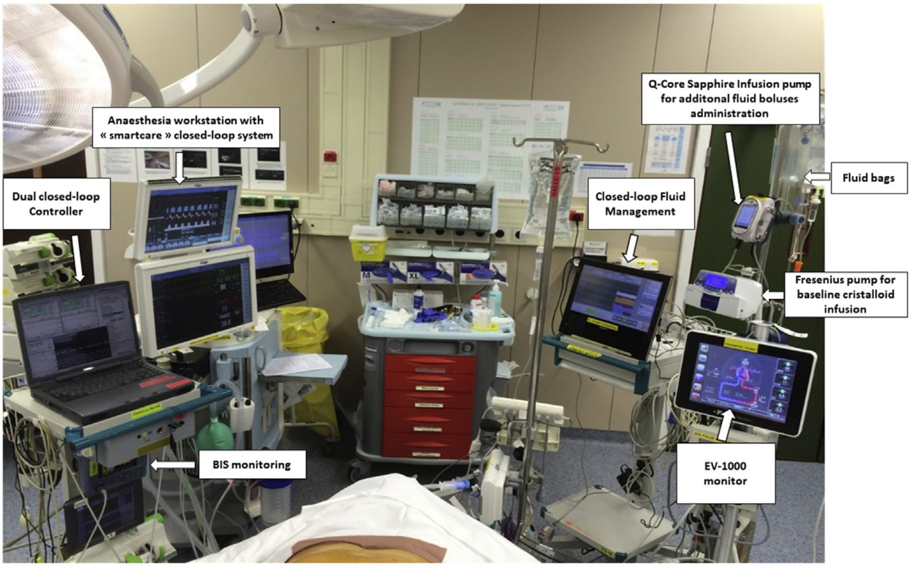

Fig. 1. Presents our operating room in Erasme Hospital, Brussels, Belgium, where the entire anesthetic was managed using several closed-loop systems operating in parallel.

Specific potential and realized closed-loop hemodynamic management systems

Fluid therapy

Fluid therapy was actually one of the earliest interventions to be automated by researchers. In the 1970s, a group in Utah linked a fluid pump to an electronic measurement of urine output [42,43]. Since then, a variety of measures have been used to guide fluid therapy including blood pressure [44,45], near-infrared spectroscopy [46], dynamic predictors of fluid responsiveness [47], or a combination of hemodynamic variables [48].

The algorithmic approach used by many goal-directed fluid therapy (GDFT) protocols [49–51] lends itself quite naturally to computer implementation. The authors of the present review have performed multiple clinical studies using such a closed-loop GDFT algorithm and have shown increased protocol compliance [52–54], decreased length of hospital stay [53], and decreased postoperative complications [55] in a variety of clinical settings. Table 1 summarizes studies performed with our recent closed-loop system for fluid administration.

Many groups are currently working on closed-loop fluid resuscitation algorithms, and this is a space that is likely to grow rapidly in the coming years [41,56–58]. Other groups are also exploring the co-application of anesthesia closed-loop systems with fluid management systems [59,60]. These systems do not yet coordinate actions to work cooperatively but have been shown to function without interference, an important safety step [59,60]. Finally, closed-loop fluid delivery systems have also been used as unbiased interventionalists in studies examining the effects of different resuscitation fluids [61,62]. Table 1 summarizes all the studies performed with our closed-loop fluid administration system over the past 8 years.

Vasopressor

Vasopressor administration, having a single “controlled” physiological variable readily measured with arterial blood pressure, is another intervention that saw early efforts in automation [63–65]. As stated above, there is a substantial amount of evidence indicating the importance of blood pressure control in the OR and ICU, while there is also limited evidence that the manual titration of vasopressors is inefficient and inaccurate [20]. This combination indicates that development of a clinical solution

Table 1
Studies performed with our closed-loop fluid administration system.

Author	Pub Date	Institution(s)	# of Participants	Main Findings
Joosten et al. [52]	Sept 2018	Erasme University Hospital, Brussels, Belgium	208	Closed-loop GDFT protocol was superior in complications and LOS when compared with no GDFT protocol
Joosten et al. [86]	Jun 2018	Erasme University Hospital, Brussels, Belgium	40	Closed-loop GDFT had similar cardiovascular endpoints as those of protocolized fluid therapy
Joosten et al. [59]	May 2018	Erasme University Hospital, Brussels, Belgium	13	Combining closed-loop GDFT with closed-loop hypnosis/Analgesia is feasible
Joosten et al. [61]	Jan 2018	Erasme University Hospital, Brussels, Belgium	160	Closed-loop GDFT systems were used to compare colloid and crystalloid, with colloid having less morbidity
Lilot et al. [41]	Jan 2018	Lyon University Hospital, Lyon, France	46	Cardiac index increased more in the closed-loop group versus manual control, otherwise no differences were noted
Joosten et al. [60]	Dec 2016	Erasme University Hospital, Brussels, Belgium	1 (case report)	Dual closed-loop systems (hypnosis and GDFT control) are possible
Joosten et al. [54]	Jun 2015	University of California, Irvine, USA	13	Intraoperative closed-loop GDFT control using a noninvasive advanced hemodynamic monitoring device is feasible
Rinehart et al. [53]	Mar 2015	University of California, Irvine, USA	50	The closed-loop GDFT control group spent more time in a preload independent state than the manual GDFT group
Rinehart et al. [87]	Mar 2014	CHU Pitié Salpêtrière, Paris, France and UC Irvine, USA	12	Closed-loop GDFT control is possible and reproducible
Rinehart et al. [88]	Nov 2013	University of California, Irvine, USA	16 (Porcine)	Closed-loop GDFT control during hemorrhage is effective with low variability
Rinehart et al. [48]	Oct 2012	University of California, Irvine, USA	NA (Simulation)	Closed-loop GDFT control of simulated patient hemorrhages outperforms manual control
Rinehart et al. [47]	Nov 2011	University of California, Irvine, USA	NA (Simulation)	Closed-loop system is an effective volumetric resuscitator in simulated hemorrhage scenarios and improved physician management of the simulated hemorrhages.

Pub Date: publication date; NA: Not applicable; GDFT: Goal-directed fluid therapy.

may be particularly impactful and be the future for blood pressure management in both surgical and ICU patients [66,67].

There was a slowdown where the medical community lost interest in these systems, but as of the last 5–8 years, a number of research groups have shown renewed interest. Modern systems are currently being developed for operating and ICU use [68–70], obstetrics and spinal-induced hypotension [71–73], and septic shock [74]. Moreover, one group in Paris is beginning to analyze the natural combination of vasopressor plus fluid administration systems with promising results [75].

Cardiac function

Cardiac function has not been as prolifically studied as a topic for closed-loop pharmacological interventions. This may be a natural result of the types of effects most often sought in cardiac medication (slowing the rate and increasing inotropy), as many drugs have nonlinear effects and ceiling effects are common and often occur at low rates. The expected exception to this is implantable cardiac pacemakers, which are apparently quite advanced and contain many layers of control algorithms governing their operation [76].

That being said, there are groups that have explored pharmacological rate control through closed-loop algorithms [77], particularly in the setting of cardiac stress tests where isoproterenol is often used, although other drugs have been trialed [78]. Studies have also been performed in inotropes [79,80].

Vasodilator

Vasodilators, such as vasopressors, have a natural and easily monitored control variable in arterial pressure and was another very early system prototyped [81]. Despite this, relatively few studies have analyzed vasodilator titration, possibly due to the relative rarity of need for vasodilation drips and the risk of overtreatment. Two studies studied automatic titration through closed-loop technologies for intracranial surgery [82] and following open-heart surgery [83].

From closed-loop therapy to predictive therapy

While computers are adept at automatically and quickly reacting to abrupt hemodynamic changes, they have the potential for even more advantageous functions when paired with predictive analytics. As computational power continues to expand, recent research has demonstrated that complex algorithms validated with large clinical data sets have the ability to predict periods of hemodynamic compromise before they occur. One significant approach is a recent study by *Hatib* et al. demonstrating that high-resolution analysis of arterial line tracings can be analyzed to produce a variable known as a "hypotension predictive index." This index was shown to predict hypotension 15 min before its occurrence in 84% of hypotensive episodes [84]. Another group also demonstrated the ability of machine learning to predict postinduction hypotension with similar efficacy [85]. This technique is very exciting and has the potential to revolutionize the influence that computational systems have on patient care and outcomes. Outside of the healthcare industry, predictive algorithms work together with autonomous systems to adjust titration of an output. In the future, it is likely that personalized titration of drugs will be administered by intelligent systems using data previously gathered from patients with similar demographics. These systems would be able to more accurately predict the response of a given patient to specific drugs and use these predictive models within their treatment protocols. This would allow for true *precision medicine*. Finally, artificial intelligence and advanced analytics will be used to better understand the interactions between various closed-loop systems working together and will help refine the way these systems work.

Summary

In summary, the clinical benefits for establishing and ensuring proper adherence to GDHT protocols are well established, and automation (closed- and open-loop systems) increases adherence to such protocols while also decreasing hemodynamic variability. Closed-loop hemodynamic systems have focused on fluid and vasopressor management, although other interventions have been evaluated. Finally, novel research systems combining multiple automated systems together and others using predictive analytics are strong areas of future investigation, although all aspects of automated hemodynamic systems have a dire need for additional research.

Practice points

- Closed-loop hemodynamic systems are evolving at an unprecedented pace and increase compliance to goal-directed strategies, although having the potential to improve outcomes when compared to manually controlled systems.
- Closed-loop systems should be seen as an aid to the clinicians. The authors and developers of these systems strive to provide solutions to make the perioperative setting ever safer and more consistent for our patients.

Research agenda

- The major research priorities moving forward would be to increase understanding and acceptance of closed-loop systems while also testing their safety and efficacy in a wider variety of hemodynamic (and other) clinical settings.
- The interaction between multiple closed-loop systems will also be an important hurdle for the growth of various automated systems.
- Regulatory pathways and acceptance by clinicians are going to be the next challenge.

Role of the funding source

No funding was received for the present manuscript.

Authors' conflicts of interest

Drs. Joseph Rinehart, Maxime Cannesson, and Alexandre Joosten are consultants for Edwards Lifesciences. Maxime Cannesson and Joseph Rinehart have ownership interest in Sironis, and Sironis has developed a fluid closed-loop system that has been licensed to Edwards Lifesciences. Maxime Cannesson is funded by the NIH under four mechanisms related to closed-loop systems (U54HL119893) and machine learning applied to healthcare data (GM117622; NR013012; and HL144692).

The other authors declare that they have no conflicts of interest concerning this article.

Acknowledgments

NA.

References

[1] Squara P, Bennett D, Perret C. Pulmonary artery catheter: does the problem lie in the users? Chest 2002;121(6):2009–15.
[2] Joosten A, Desebbe O, Suehiro K, et al. Impact of advanced monitoring variables on intraoperative clinical decision-making: an international survey. J Clin Monit Comput 2017;31(1):205–12.
[3] Lugo G, Arizpe D, Domínguez G, et al. Relationship between oxygen consumption and oxygen delivery during anesthesia in high-risk surgical patients. Crit Care Med 1993;21(1):64–9.
[4] Lobo S. Effects of "Restrictive" and "Liberal" strategies of intra-operative fluid management during optimisation of oxygen delivery in high-risk surgical patients. 2013. http://isrctnorg/.
[5] Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. JAMA 2014;311(21):2181–90.
[6] Pestaña D, Espinosa E, Eden A, et al. Perioperative goal-directed hemodynamic optimization using noninvasive cardiac output monitoring in major abdominal surgery: a prospective, randomized, multicenter, pragmatic trial: POEMAS Study (PeriOperative goal-directed thErapy in Major Abdominal Surgery). Anesth Analg 2014;119(3):579–87.
[7] Brandstrup B, Svendsen PE, Rasmussen M, et al. Which goal for fluid therapy during colorectal surgery is followed by the best outcome: near-maximal stroke volume or zero fluid balance? Br J Anaesth 2012;109(2):191–9.
[8] Pearse R, Dawson D, Fawcett J, et al. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. Crit Care 2005;9(6):R687–93.
[9] Rhodes A, Cecconi M, Hamilton M, et al. Goal-directed therapy in high-risk surgical patients: a 15-year follow-up study. Intensive Care Med 2010;36(8):1327–32.
[10] Calvo-Vecino JM, Ripollés-Melchor J, Mythen MG, et al. Effect of goal-directed haemodynamic therapy on postoperative complications in low-moderate risk surgical patients: a multicentre randomised controlled trial (FEDORA trial). Br J Anaesth 2018;120(4):734–44.
*[11] Cannesson M, Ramsingh D, Rinehart J, et al. Perioperative goal-directed therapy and postoperative outcomes in patients undergoing high-risk abdominal surgery: a historical-prospective, comparative effectiveness study. Crit Care 2015;19:261.
[12] Jin J, Min S, Liu D, et al. Clinical and economic impact of goal-directed fluid therapy during elective gastrointestinal surgery. Perioper Med (Lond) 2018;7:22.
[13] Russo A, Aceto P, Grieco DL, et al. Goal-directed hemodynamic management in patients undergoing primary debulking gynaecological surgery: a matched-controlled precision medicine study. Gynecol Oncol 2018;151(2):299–305.

[14] Lima MF, Mondadori LA, Chibana AY, et al. Outcome impact of hemodynamic and depth of anesthesia monitoring during major cancer surgery: a before-after study. J Clin Monit Comput 2018;33(3):365–71. https://doi.org/10.1007/s10877-018-0190-8. Epub 2018 Aug 3.
[15] Asfar P, Meziani F, Hamel J-F, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med 2014;370(17):1583–93.
[16] Lamontagne F, Cook DJ, Meade MO, et al. Vasopressor use for severe hypotension—a multicentre prospective observational study. PLoS One 2017;12(1):e0167840.
[17] Maheshwari K, Nathanson BH, Munson SH, et al. The relationship between ICU hypotension and in-hospital mortality and morbidity in septic patients. Intensive Care Med 2018 Jun;44(6):857–67. https://doi.org/10.1007/s00134-018-5218-5. Epub 2018 Jun 5.
[18] Jinadasa SP, Mueller A, Prasad V, et al. Blood pressure coefficient of variation and its association with cardiac surgical outcomes. Anesth Analg 2018 Oct;127(4):832–9. https://doi.org/10.1213/ANE.0000000000003362.
[19] Sessler DI, Turan A, Stapelfeldt WH, et al. Triple-low alerts do not reduce mortality: a real-time randomized trial. Anesthesiology 2019 Jan;130(1):72–82. https://doi.org/10.1097/ALN.0000000000002480.
[20] Rinehart J, Ma M, Calderon MD, et al. Blood pressure variability in surgical and intensive care patients: is there a potential for closed-loop vasopressor administration? Anaesth Crit Care Pain Med 2019;38(1):69–71.
[21] Stapelfeldt WH, Yuan H, Dryden JK, et al. The SLU score: a novel method for detecting hazardous hypotension in adult patients undergoing noncardiac surgical procedures. Anesth Analg 2017 Apr;124(4):1135–52. https://doi.org/10.1213/ANE.0000000000001797.
[22] Salmasi V, Maheshwari K, Yang D, et al. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: a retrospective cohort analysis. Anesthesiology 2017;126(1):47–65.
[23] Futier E, Lefrant JY, Guinot PG, et al. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. JAMA 2017;318(14):1346–57.
[24] van Waes JA, van Klei WA, Wijeysundera DN, et al. Association between intraoperative hypotension and myocardial injury after vascular surgery. Anesthesiology 2016;124(1):35–44.
[25] Sessler DI, Meyhoff CS, Zimmerman NM, et al. Period-dependent associations between hypotension during and for four days after noncardiac surgery and a composite of myocardial infarction and death: a substudy of the POISE-2 trial. Anesthesiology 2018;128(2):317–27.
[26] Townsend SR, Tefera L, Rivers EP. Evidence underpinning the centers for medicare & medicaid services' severe sepsis and septic shock management bundle (SEP-1). Ann Intern Med 2018 Apr 17;168(8):609–10. https://doi.org/10.7326/L18-0139.
[27] Yapps B, Shin S, Bighamian R, et al. Hypotension in ICU patients receiving vasopressor therapy. Sci Rep 2017;7(1):8551.
[28] Vincent JL, Nielsen ND, Shapiro NI, et al. Mean arterial pressure and mortality in patients with distributive shock: a retrospective analysis of the MIMIC-III database. Ann Intensive Care 2018;8(1):107.
[29] Nguyen DN, Huyghens L, Parra J, et al. Hypotension and a positive fluid balance are associated with delirium in patients with shock. PLoS One 2018;13(8):e0200495.
[30] Thacker JK, Mountford WK, Ernst FR, et al. Perioperative fluid utilization variability and association with outcomes: considerations for enhanced recovery efforts in sample US surgical populations. Ann Surg 2016;263(3):502–10.
[31] Lilot M, Ehrenfeld JM, Lee C, et al. Variability in practice and factors predictive of total crystalloid administration during abdominal surgery: retrospective two-centre analysis. Br J Anaesth 2015;114(5):767–76.
[32] Shin CH, Long DR, McLean D, et al. Effects of intraoperative fluid management on postoperative outcomes: a hospital registry study. Ann Surg 2018;267(6):1084–92.
[33] Minto G, Mythen MG. Perioperative fluid management: science, art or random chaos? Br J Anaesth 2015;114(5):717–21.
[34] Spanjersberg WR, Bergs EA, Mushkudiani N, et al. Protocol compliance and time management in blunt trauma resuscitation. Emerg Med J 2009;26(1):23–7.
[35] Godier A, Bacus M, Kipnis E, et al. Compliance with evidence-based clinical management guidelines in bleeding trauma patients. Br J Anaesth 2016;117(5):592–600.
[36] Lipton JA, Barendse RJ, Schinkel AFL, et al. Impact of an alerting clinical decision support system for glucose control on protocol compliance and glycemic control in the intensive cardiac care unit. Diabetes Technol Ther 2011;13(3):343–9.
[37] Gustafsson UO. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. Arch Surg 2011;146(5):571.
[38] Bakker N, Cakir H, Doodeman HJ, et al. Eight years of experience with Enhanced Recovery after Surgery in patients with colon cancer: impact of measures to improve adherence. Surgery 2015;157(6):1130–6.
*[39] Pasin L, Nardelli P, Pintaudi M, et al. Closed-loop delivery systems versus manually controlled administration of total IV anesthesia: a meta-analysis of randomized clinical trials. Anesth Analg 2017;124(2):456–64.
*[40] Brogi E, Cyr S, Kazan R, et al. Clinical performance and safety of closed-loop systems: a systematic review and meta-analysis of randomized controlled trials. Anesth Analg 2017;124(2):446–55.
*[41] Lilot M, Bellon A, Gueugnon M, et al. Comparison of cardiac output optimization with an automated closed-loop goal-directed fluid therapy versus non standardized manual fluid administration during elective abdominal surgery: first prospective randomized controlled trial. J Clin Monit Comput 2018;32(6):993–1003.
[42] Bowman RJ, Westenskow DR. A microcomputer-based fluid infusion system for the resuscitation of burn patients. IEEE Trans Biomed Eng 1981;28(6):475–9.
[43] DeBey RK, Westenskow DR, Jordan WS, et al. A urine based control system for fluid infusion. Biomed Sci Instrum 1987;23:195–8.
[44] Blankenship HB, Wallace FD, Pacifico AD. Clinical application of closed-loop postoperative autotransfusion. Med Prog Technol 1990;16(1–2):89–93.
[45] Hoskins SL, Elgjo GI, Lu J, et al. Closed-loop resuscitation of burn shock. J Burn Care Res – Offic Publ Am Burn Assoc 2006;27(3):377–85.

[46] Chaisson NF, Kirschner RA, Deyo DJ, et al. Near-infrared spectroscopy-guided closed-loop resuscitation of hemorrhage. J Trauma 2003;54(5 Suppl):S183–92.
[47] Rinehart J, Alexander B, Le Manach Y, et al. Evaluation of a novel closed-loop fluid-administration system based on dynamic predictors of fluid responsiveness: an in silico simulation study. Crit Care (Lond, Engl) 2011;15(6):R278.
[48] Rinehart J, Chung E, Canales C, et al. Intraoperative stroke volume optimization using stroke volume, arterial pressure, and heart rate: closed-loop (learning intravenous resuscitator) versus anesthesiologists. J Cardiothorac Vasc Anesth 2012; 26(5):933–9.
[49] Rollins KE, Lobo DN. Intraoperative goal-directed fluid therapy in elective major abdominal surgery: a meta-analysis of randomized controlled trials. Ann Surg 2016;263(3):465–76.
[50] Ripolles-Melchor J, Espinosa A, Martinez-Hurtado E, et al. Perioperative goal-directed hemodynamic therapy in noncardiac surgery: a systematic review and meta-analysis. J Clin Anesth 2016;28:105–15.
[51] Ramsingh DS, Sanghvi C, Gamboa J, et al. Outcome impact of goal directed fluid therapy during high risk abdominal surgery in low to moderate risk patients: a randomized controlled trial. J Clin Monit Comput 2013;27(3):249–57.
*[52] Joosten A, Coeckelenbergh S, Delaporte A, et al. Implementation of closed-loop-assisted intra-operative goal-directed fluid therapy during major abdominal surgery: a case-control study with propensity matching. Eur J Anaesthesiol 2018;35(9): 650–8.
*[53] Rinehart J, Lilot M, Lee C, et al. Closed-loop assisted versus manual goal-directed fluid therapy during high-risk abdominal surgery: a case-control study with propensity matching. Crit Care (Lond, Engl) 2015;19:94.
*[54] Joosten A, Huynh T, Suehiro K, et al. Goal-Directed fluid therapy with closed-loop assistance during moderate risk surgery using noninvasive cardiac output monitoring: a pilot study. Br J Anaesth 2015;114(6):886–92.
*[55] Joosten A, Hafiane R, Pustetto M, et al. Practical impact of a decision support for goal-directed fluid therapy on protocol adherence: a clinical implementation study in patients undergoing major abdominal surgery. J Clin Monit Comput 2019 Feb;33(1):15–24. https://doi.org/10.1007/s10877-018-0156-x. Epub 2018 May 19.
[56] Jin X, Bighamian R, Hahn JO. Development and in silico evaluation of a model-based closed-loop fluid resuscitation control algorithm. IEEE Trans Bio Medical Eng 2018 Nov 19. https://doi.org/10.1109/TBME.2018.2880927 [Epub ahead of print].
[57] Gholami B, Haddad WM, Bailey JM, et al. A pilot study evaluating adaptive closed-loop fluid resuscitation during states of absolute and relative hypovolemia in dogs. J Vet Emerg Crit Care (San Antonio) 2018;28(5):436–46.
[58] Hundeshagen G, Kramer GC, Ribeiro Marques N, et al. Closed-loop- and decision-assist-guided fluid therapy of human hemorrhage. Crit Care Med 2017;45(10):e1068–74.
[59] Joosten A, Jame V, Alexander B, et al. Feasibility of fully automated hypnosis, analgesia, and fluid management using 2 independent closed-loop systems during major vascular surgery: a pilot study. Anesth Analg 2018.
*[60] Joosten A, Delaporte A, Cannesson M, et al. Fully automated anesthesia and fluid management using multiple physiologic closed-loop systems in a patient undergoing high-risk surgery. A A Case Rep 2016;7(12):260–5.
*[61] Joosten A, Delaporte A, Ickx B, et al. Crystalloid versus colloid for intraoperative goal-directed fluid therapy using a closed-loop system: a randomized, double-blinded, controlled trial in major abdominal surgery. Anesthesiology 2018;128(1):55–66.
[62] Joosten A, Delaporte A, Mortier J, et al. Long-term impact of crystalloid versus colloid solutions on renal function and disability-free survival after major abdominal surgery. Anesthesiology 2019;130(2):227–36.
[63] Packer JS, Mason DG, Cade JF, et al. An adaptive controller for closed-loop management of blood pressure in seriously ill patients. IEEE Trans Biomed Eng 1987;34(8):612–6.
[64] Mason DG, Packer JS, Cade JF, et al. Closed-loop management of blood pressure in critically ill patients. Australas Phys Eng Sci Med 1985;8(4):164–7.
[65] Potter DR, Moyle JT, Lester RJ, et al. Closed loop control of vasoactive drug infusion. A preliminary report. Anaesthesia 1984;39(7):670–7.
[66] Michard F, Liu N, Kurz A. The future of intraoperative blood pressure management. J Clin Monit Comput 2018;32(1):1–4.
[67] Joosten A, Rinehart J. Part of the steamroller and not part of the road: better blood pressure management through automation. Anesth analgesia 2017;125(1):20–2.
[68] Rinehart J, Joosten A, Ma M, et al. Closed-loop vasopressor control: in-silico study of robustness against pharmacodynamic variability. J Clin Monit Comput 2018 Dec 11. https://doi.org/10.1007/s10877-018-0234-0 [Epub ahead of print].
[69] Rinehart J, Ma M, Calderon MD, et al. Feasibility of automated titration of vasopressor infusions using a novel closed-loop controller. J Clin Monit Comput 2018 Feb;32(1):5–11. https://doi.org/10.1007/s10877-017-9981-6. ?Epub 2017 Jan 25.
[70] Joosten A, Delaporte A, Alexander B, et al. Automated titration of vasopressor infusion using a closed-loop controller: in vivo feasibility study using a swine model. Anesthesiology 2019 Mar;130(3):394–403. https://doi.org/10.1097/ALN.0000000000002581.
[71] Ngan Kee WD, Tam YH, Khaw KS, et al. Closed-loop feedback computer-controlled phenylephrine for maintenance of blood pressure during spinal anesthesia for cesarean delivery: a randomized trial comparing automated boluses versus infusion. Anesth Analg 2017 Jul;125(1):117–23. https://doi.org/10.1213/ANE.0000000000001974.
[72] Ngan Kee WD, Khaw KS, Tam YH, et al. Performance of a closed-loop feedback computer-controlled infusion system for maintaining blood pressure during spinal anaesthesia for caesarean section: a randomized controlled comparison of norepinephrine versus phenylephrine. J Clin Monit Comput 2017;31(3):617–23.
[73] Ngan Kee WD, Tam YH, Khaw KS, et al. Closed-loop feedback computer-controlled infusion of phenylephrine for maintaining blood pressure during spinal anaesthesia for caesarean section: a preliminary descriptive study. Anaesthesia 2007;62(12):1251–6.
[74] Merouani M, Guignard B, Vincent F, et al. Norepinephrine weaning in septic shock patients by closed loop control based on fuzzy logic. Crit Care 2008;12(6):R155.
[75] Libert N, Chenegros G, Harrois A, et al. Performance of closed-loop resuscitation of haemorrhagic shock with fluid alone or in combination with norepinephrine: an experimental study. Ann Intensive Care 2018;8(1):89.
[76] Tjong FV, Reddy VY. Permanent leadless cardiac pacemaker therapy: a comprehensive review. Circulation 2017;135(15): 1458–70.

[77] Sarabadani Tafreshi A, Klamroth-Marganska V, Nussbaumer S, et al. Real-time closed-loop control of human heart rate and blood pressure. IEEE Trans Biomed Eng 2015;62(5):1434–42.

[78] Valcke CP, Chizeck HJ. Closed-loop drug infusion for control of heart-rate trajectory in pharmacological stress tests. IEEE Trans Biomed Eng 1997;44(3):185–95.

[79] Uemura K, Kawada T, Zheng C, et al. Less invasive and inotrope-reduction approach to automated closed-loop control of hemodynamics in decompensated heart failure. IEEE Trans Biomed Eng 2016;63(8):1699–708.

[80] Osswald S, Cron T, Gradel C, et al. Closed-loop stimulation using intracardiac impedance as a sensor principle: correlation of right ventricular dP/dtmax and intracardiac impedance during dobutamine stress test. Pacing Clin Electrophysiol 2000;23(10 Pt 1):1502–8.

[81] Hammond JJ, Kirkendall WM, Calfee RV. Hypertensive crisis managed by computer controlled infusion of sodium nitroprusside: a model for the closed loop administration of short acting vasoactive agents. Comput Biomed Res 1979; 12(2):97–108.

[82] Mackenzie AF, Colvin JR, Kenny GN, et al. Closed loop control of arterial hypertension following intracranial surgery using sodium nitroprusside. A comparison of intra-operative halothane or isoflurane. Anaesthesia 1993;48(3):202–4.

[83] Bednarski P, Siclari F, Voigt A, et al. Use of a computerized closed-loop sodium nitroprusside titration system for antihypertensive treatment after open heart surgery. Crit Care Med 1990;18(10):1061–5.

[84] Hatib F, Jian Z, Buddi S, et al. Machine-learning algorithm to predict hypotension based on high-fidelity arterial pressure waveform analysis. Anesthesiology 2018;129(4):663–74.

[85] Kendale S, Kulkarni P, Rosenberg AD, et al. Supervised machine-learning predictive analytics for prediction of postinduction hypotension. Anesthesiology 2018;129(4):675–88.

[86] Joosten A, Raj Lawrence S, Colesnicenco A, et al. Personalized versus protocolized fluid management using noninvasive hemodynamic monitoring (clearsight system) in patients undergoing moderate-risk abdominal surgery. Anesth Analg 2018 Jun 5. https://doi.org/10.1213/ANE.0000000000003553 [Epub ahead of print].

[87] Rinehart J, Le Manach Y, Douiri H, et al. First closed-loop goal directed fluid therapy during surgery: a pilot study. Ann francaises d'anesthesie et de reanimation 2014;33(3):e35–41.

[88] Rinehart J, Lee C, Canales C, et al. Closed-loop fluid administration compared to anesthesiologist management for hemodynamic optimization and resuscitation during surgery: an in vivo study. Anesth Analg 2013;117(5):1119–29.